Effect of Beta-blocker Treatment on V˙O2peak in Patients with Heart Failure

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Abstract: PURPOSE In addition to prolonged life and reduced hospitalization rates, it is currently unclear whether beta-blocker (BB) treatment modulates peak oxygen consumption (V˙O2peak), a hallmark of exercise capacity, in patients with heart failure (HF). The main aim of this study is to determine the effect of BB treatment on V˙O2peak in HF patients. METHODS We conducted a systematic search of MEDLINE, Scopus, and Web of Science since their inceptions until March 2017 for randomized controlled trials (RCT) assessing the effect of BB treatment on V˙O2peak in chronic HF patients. A meta-analysis was performed to ascertain the standardized mean difference (SMD) between the effects of BB and placebo treatment on V˙O2peak. Secondary outcomes included peak exercise performance and New York Health Association functional class. Subgroup and meta-regression analyses assessed potential moderating factors. RESULTS Fourteen RCT met the inclusion criteria (overall n = 616). Interventions comprised BB (n = 324) or placebo (n = 292) administration lasting 3 to 24 months. Concomitant reported medication did not differ between HF patients assigned to BB and placebo groups. After data pooling, V˙O2peak was preserved with BB compared with placebo treatment (SMD, -0.04; 95% confidence interval (CI), -0.20 to 0.12; P = 0.61); heterogeneity among studies was not detected (I = 0%, P = 0.88). Peak exercise performance was not altered (SMD, 0.02; 95% CI, -0.16 to 0.20; P = 0.85), whereas New York Health Association functional class was reduced with BB compared with placebo (SMD, -0.54; 95% CI, -0.90 to -0.18; P = 0.003). CONCLUSIONS According to evidence from RCT, prolonged BB (B1-selective or nonselective) treatment does not affect V˙O2peak but improves functional status in HF patients.

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Effect of Beta-blocker Treatment on $\dot{V}O_{2peak}$ in Patients with Heart Failure

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ABSTRACT

MONTERO, D., and A. J. FLAMMER. Effect of Beta-blocker Treatment on $\dot{V}O_{2peak}$ in Patients with Heart Failure. *Med. Sci. Sports Exerc.*, Vol. 50, No. 5, pp. 889–896, 2018. **Purpose**: In addition to prolonged life and reduced hospitalization rates, it is currently unclear whether beta-blocker (BB) treatment modulates peak oxygen consumption ($\dot{V}O_{2peak}$), a hallmark of exercise capacity, in patients with heart failure (HF). The main aim of this study is to determine the effect of BB treatment on $\dot{V}O_{2peak}$ in HF patients. **Methods**: We conducted a systematic search of MEDLINE, Scopus, and Web of Science since their inceptions until March 2017 for randomized controlled trials (RCT) assessing the effect of BB treatment on $\dot{V}O_{2peak}$ in chronic HF patients. A meta-analysis was performed to ascertain the standardized mean difference (SMD) between the effects of BB and placebo treatment on $\dot{V}O_{2peak}$. Secondary outcomes included peak exercise performance and New York Health Association functional class. Subgroup and meta-regression analyses assessed potential moderating factors. **Results**: Fourteen RCT met the inclusion criteria (overall $n = 616$). Interventions comprised BB ($n = 324$) or placebo ($n = 292$) administration lasting 3 to 24 months. Concomitant reported medication did not differ between HF patients assigned to BB and placebo groups. After data pooling, $\dot{V}O_{2peak}$ was preserved with BB compared with placebo treatment (SMD, −0.04; 95% confidence interval (CI), −0.20 to 0.12; $P = 0.61$); heterogeneity among studies was not detected ($I^2 = 0\%$, $P = 0.88$). Peak exercise performance was not altered (SMD, 0.02; 95% CI, −0.16 to 0.20; $P = 0.85$), whereas New York Health Association functional class was reduced with BB compared with placebo (SMD, −0.54; 95% CI, −0.90 to −0.18; $P = 0.003$). **Conclusions**: According to evidence from RCT, prolonged BB (B_1-selective or nonselective) treatment does not affect $\dot{V}O_{2peak}$ but improves functional status in HF patients. **Key Words:** BETA-BLOCKER THERAPY, EXERCISE CAPACITY, HEART FAILURE, META-ANALYSIS

A memorable challenge to the paradigm for the treatment of heart failure (HF) materialized in the 1970s (1,2). Beta-blockers (BB) were first administered in HF patients by Swedish scientists relying on consistent basic and clinical evidence (1,3–7), yet against the prevailing doctrine. At the present time, chronic neurohormonal activation is a fundamental concept to understand the mechanisms of disease progression and treatment of HF (8). BB counterbalance beta-adrenergic activation leading to partial normalization of increased resting heart rate, filling pressure, and afterload, collectively blunting the deleterious effect of persistent hemodynamic stress (9). The beneficial influence of BB treatment on primary end points such as survival and HF-related hospitalization has been established by large randomized controlled trials (RCT) (10–13). Beyond these unequivocal long-term gains, it seems reasonable to question about the functional effects of BB treatment, particularly because the prognosis of HF patients remains poor (14–16).

Peak oxygen consumption ($\dot{V}O_{2peak}$), as elicited by incremental dynamic exercise (treadmill, bicycle ergometer), is hallmark of exercise capacity commonly used to determine eligibility for cardiac transplantation. Irrespective of the stage of disease, HF patients are characterized by impaired $\dot{V}O_{2peak}$ (<80% predicted) (17–29). $\dot{V}O_{2peak}$ is a function of stroke volume (SV), peak heart rate (HR_{peak}), and oxygen (O_2) extraction, conforming to the Fick principle: $\dot{V}O_{2peak} = SV \times HR_{peak} \times$ arteriovenous O_2 difference (30). Among the Fick determinants of $\dot{V}O_{2peak}$, SV is substantially decreased in HF patients compared with control individuals (31,32). Moreover, BB treatment specifically limits HR_{peak}, reaching up to 25% decrements (17–20,22–24,26,28,29). Given that cardiac output ($SV \times HR_{peak}$), through the regulation of convective O_2 delivery, predominantly determines $\dot{V}O_{2peak}$, this could be compromised by BB administration. However, RCT studies assessing the effect of BB on $\dot{V}O_{2peak}$ or peak exercise performance as a surrogate have had small sample sizes and have reported conflicting results (17–29,33–46). Furthermore, efforts to synthesize a fraction of previous RCT published until 2005 have delivered varied conclusions (47). Therefore, the primary purpose of this study was to perform a systematic review and meta-analysis of RCT assessing the

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effect of prolonged BB treatment on $\dot{V}O_{2peak}$ in HF patients, as well as to determine the influence of potential clinical and methodological moderating factors.

METHODS

The review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (48).

Data sources and searches. The systematic search included MEDLINE, Scopus, and Web of Science since their inceptions until March 2017. We used combinations of the subject headings "heart failure," "beta-blocker," "peak," "oxygen consumption," and "exercise capacity"; the search strategy for MEDLINE is shown in Figure, Supplemental Digital Content 1, MEDLINE search strategy, http://links.lww.com/MSS/B129. We also performed hand searching in reference citations of identified reviews, articles included in meta-analysis, and related citations in MEDLINE and Google Scholar.

Article selection. To be included in the analysis, an original research article had to meet the following criteria: 1) RCT involving HF patients, 2) $\dot{V}O_{2peak}$ reported before and after BB treatment, and 3) duration of intervention of ≥1 month. In the event of multiple publications pertaining to the same research, the most comprehensive report was included. Inclusion of articles was not limited by publication status or language.

Data extraction and quality assessment. The following variables were summarized in a preformatted spreadsheet: authors, year of publication, characteristics of study participants (*n*, age, sex, height, weight, New York Health Association (NYHA) functional class, inclusion/exclusion criteria, heart rate, left ventricular end-diastolic volume, left ventricular ejection fraction (LVEF), blood pressure, smoking status, comorbidities, medication), BB treatment (agent, type, dose, duration), and exercise capacity (methodology, $\dot{V}O_{2peak}$, peak exercise performance). The methodological quality of each included study was assessed by the established Jadad scale (49).

Data synthesis and analysis. The meta-analysis was performed using Review Manager software (RevMan 5.3; Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-analysis software (Biostat, Englewood, NJ). The primary outcome was the standardized mean difference (SMD) between the effects of BB and placebo treatment on $\dot{V}O_{2peak}$. Secondary outcomes included the effects of BB versus placebo treatment on peak exercise performance (as determined by peak incremental exercise time or power output) and NYHA functional class. If the variability of change (i.e., standard deviation of change (SD_c)) for a given outcome was not reported, the formula

$$SD_c = \sqrt{[(SD_{pre})^2 + (SD_{post})^2 - (2 \times corr_{pre,post} \times SD_{pre} \times SD_{post})]}$$

was applied (50). SD_{pre}, SD_{post}, and $corr_{pre,post}$ represent the standard deviation of the preintervention value, the standard deviation of the postintervention value, and the correlation coefficient between preintervention and postintervention values, respectively. The $corr_{pre,post}$ was conservatively set at 0.5. Each SMD was weighted by the inverse variance, and it was pooled with a random-effects model (51). Heterogeneity among studies was assessed using the chi-squared test for heterogeneity and I^2 statistics.

Potential moderating factors influencing the SMD in $\dot{V}O_{2peak}$ were evaluated by using subgroup analysis comparing studies grouped by qualitative variables (agent/type of BB treatment, methodology of exercise testing). In addition, meta-regression analyses were performed to determine the association between the SMD in $\dot{V}O_{2peak}$ and potential moderating quantitative variables (sample size, age, sex, body mass index, heart rate, left ventricular end-diastolic volume, LVEF, blood pressure, baseline NYHA functional class, prevalence of medication, baseline $\dot{V}O_{2peak}$, year of publication, methodological quality score). In all meta-regression models, studies were weighted by the inverse variance of the dependent variable. Potential moderating factors were entered as independent variables in regressions models with the SMD

TABLE 1. Main baseline characteristics of studies included in the meta-analysis.

	n		Age, yr		Female, %		LVEF, %		MAP, mm Hg		NYHA		$\dot{V}O_{2peak}$, mL·kg^{-1}·min^{-1}	
Reference	BB	PBO	BB	PBO	BB	PBO	BB	PBO	BB	PBO	BB	PBO	BB	PBO
Conraads et al. (17)	42[a]	51[a]	66 ± 10[b]	65 ± 11[b]	65[b]	64[b]	>45	>45	96	95	2.2 ± 0.4	2.2 ± 0.4	17.0 ± 4.8	17.8 ± 6.0
Norozi et al. (18)	13	21	29 ± 10	32 ± 9	15	52	57 ± 8	58 ± 10	n/a	n/a	1.6 ± 0.5	1.6 ± 0.5	22.0 ± 2.0	21.0 ± 2.0
Terzi et al. (19)	26[a]	22[a]	59 ± 10[b]	60 ± 9[b]	18[b]	25[b]	29 ± 6[b]	30 ± 7[b]	n/a	n/a	2.3 ± 0.5	2.3 ± 0.5	17.1 ± 5.2	14.4 ± 4.5
Dubach et al. (20)	13	15	55 ± 12	59 ± 10	n/a	n/a	25 ± 7	27 ± 13	96	103	2–3	2–3	18.3 ± 5.0	18.9 ± 3.6
Gullestad et al. (22)	43	40	64 ± 11	63 ± 9	26	28	26 ± 6	27 ± 6	n/a	n/a	2.6 ± 0.5	2.6 ± 0.6	15.3 ± 3.0	16.0 ± 5.7
Hulsmann et al. (21)	23	20	n/a	n/a	n/a	n/a	19 ± 5	19 ± 5	n/a	n/a	2.2 ± 0.4	2.3 ± 0.4	18.0 ± 5.0	17.0 ± 4.0
Genth-Zotz et al. (23)	26	26	53	55	31	27	27 ± 6	29 ± 10	89	96	2.4 ± 0.5	2.5 ± 0.5	13.5 ± 2.8	13.6 ± 4.8
Guazzi et al. (24)	14	7	n/a	n/a	n/a	n/a	34 ± 6	35 ± 6	n/a	n/a	2–3	2–3	16.6 ± 0.3	17.0 ± 0.5
Gilbert et al. (25)	12[a]	12[a]	53 ± 11[b]	48 ± 12[b]	n/a	n/a	23 ± 9	21 ± 8	88 ± 13	85 ± 8	2.5 ± 0.7[b]	2.6 ± 0.8[b]	18.7 ± 5.1	18.5 ± 5.1
Krum et al. (27)	33	16	56 ± 13	53 ± 14	21	25	17 ± 7	16 ± 7	88 ± 16	78 ± 10	2.8 ± 0.6	2.8 ± 0.8	14.2 ± 5.2	13.9 ± 5.2
Olsen et al. (26)	32[a]	23[a]	54 ± 12[b]	50 ± 15[b]	6[b]	8[b]	20 ± 6[b]	19 ± 5[b]	84 ± 12[b]	85 ± 5[b]	2.5 ± 0.5[b]	2.4 ± 0.5[b]	17.5 ± 4.5	17.3 ± 3.8
Metra et al. (28)	20	20	50 ± 10	52 ± 10	10	10	20 ± 7	20 ± 6	90 ± 11	91 ± 9	2.7 ± 0.5	2.8 ± 0.4	16.0 ± 4.0	15.0 ± 3.0
Woodley et al. A (29)	13	9	46 ± 11	56 ± 24*	31	33	26 ± 6	21 ± 8	89 ± 10	82 ± 20	2.4 ± 0.4	2.7 ± 0.6	20.1 ± 4.7	16.4 ± 4.2
Woodley et al. B (29)	14[a]	10[a]	54 ± 12[b]	53 ± 10[b]	25[b]	18[b]	21 ± 7[b]	18 ± 8[b]	84 ± 14[b]	84 ± 14[b]	2.7 ± 0.4[b]	2.7 ± 0.3[b]	15.7 ± 2.3	16.2 ± 4.7

Data are *n*, prevalence, mean ± SD, or range. One article presented two independent RCT studies (herein distinguished by A and B) (29).
*Significantly different from BB group at $P < 0.05$.
[a]Subsample size presenting with $\dot{V}O_{2peak}$ data.
[b]Data from primary sample size.
MAP, mean arterial pressure; n/a, data not available; PBO, placebo group.

TABLE 2. BB treatment and prevailing concomitant medication in studies included in the meta-analysis.

	BB Treatment				Concomitant Medication, %					
					ACEi		Diuretics		Digitalis	
Reference	Agent	Type	Target Dose, mg·d^{-1}	Duration, months	BB	PBO	BB	PBO	BB	PBO
Conraads et al. (17)	Nebivolol	β_1-Selective	10	6	75[a]	80[a]	49[a]	54[a]	n/a	n/a
Norozi et al. (18)	Bisoprolol	β_1-Selective	10	6	n/a	n/a	8	5	8	14
Terzi et al. (19)	Bisoprolol	β_1-Selective	5	3	100	100	82[a]	83[a]	63[a]	68[a]
Dubach et al. (20)	Bisoprolol	β_1-Selective	10	12	100	100	77	93	38	60
Gullestad et al. (22)	Metoprolol	β_1-Selective	200	11	95	90	86	85	47	45
Hulsmann et al. (21)	Atenolol	β_1-Selective	100	24	100	100	n/a	n/a	n/a	n/a
Genth-Zotz et al. (23)	Metoprolol	β_1-Selective	150	6	92	91	71	71	51	52
Guazzi et al. (24)	Carvedilol	Nonselective	50	6	n/a	n/a	100	100	100	100
Gilbert et al. (25)	Metoprolol	β_1-Selective	150	6	n/a	n/a	n/a	n/a	n/a	n/a
Krum et al. (27)	Carvedilol	Nonselective	50	3	94	88	n/a	n/a	n/a	n/a
Olsen et al. (26)	Carvedilol	Nonselective	50–100	4	100	89[a]	83[a]	79[a]	92[a]	71[a]
Metra et al. (28)	Carvedilol	Nonselective	50	4	95	100	100	100	100	100
Woodley et al. A (29)	Bucindolol	Nonselective	200	3	71	67[a]	93	89[a]	86	89[a]
Woodley et al. B (29)	Bucindolol	Nonselective	200	3	n/a	n/a	n/a	n/a	n/a	n/a

[a]Data from primary sample size.
ACEi, angiotensin-converting enzyme inhibitors; n/a, data not available; PBO, placebo group.

in $\dot{V}O_{2peak}$ as the dependent variable. Publication and/or other biases were evaluated by the Begg and Mazumdar rank correlation test and Egger regression test (52). A P value of <0.05 was considered statistically significant.

RESULTS

Study selection and characteristics. The flow diagram of the process of article selection is illustrated in Figure, Supplemental Digital Content 2, Flow diagram of the process of article selection, http://links.lww.com/MSS/B130, which resulted in the inclusion of 13 articles. One of the articles presented two independent RCT studies, each of which was evaluated as an individual study (29). Table 1 shows the main baseline characteristics of the resulting 14 studies, comprising a total of 616 chronic HF patients allocated to BB (n = 324) or placebo (n = 292) treatment. Mean NYHA functional class and $\dot{V}O_{2peak}$ ranged from 1.6 to 2.8 and from 13.5 to 22 mL·min^{-1}·kg^{-1}, respectively. Carvedilol was administered in 4 studies (n = 165), metoprolol in 3 studies (n = 159), bisoprolol in 3 studies (n = 110), nebivolol in 1 study (n = 93), bucindolol in 2 studies (n = 46), and atenolol in 1 study (n = 43), with treatment periods of ≥3 months (Table 2). Concomitant reported medication did not differ between BB and placebo groups (Table 2). All studies assessed $\dot{V}O_{2peak}$ via established incremental bicycle/treadmill exercise protocols (Table 3).

Effect of BB versus placebo treatment. BB treatment had no effect on $\dot{V}O_{2peak}$ compared with placebo (n = 616; SMD, −0.04; 95% confidence interval (CI), −0.20 to 0.12; P = 0.61) (Fig. 1). No heterogeneity was detected among studies (I^2 = 0%, P = 0.88). Subgroup analyses showed similar SMD in $\dot{V}O_{2peak}$ between studies assorted by BB treatment characteristics (agent (P = 0.47), type (P = 0.88)) and exercise testing methodology (P = 0.25). Likewise, meta-regression analyses did not reveal any influence of potential moderating quantitative variables. The effects of BB versus placebo treatment on secondary outcomes were reported in 11 studies for peak exercise performance (n = 493) and 7 studies for NYHA functional class (n = 347). In line with $\dot{V}O_{2peak}$ results, peak exercise performance did not differ with BB compared with placebo treatment (n = 493; SMD, 0.02; 95% CI, −0.16 to 0.20; P = 0.85) (Fig. 2). In contrast, NYHA functional class was improved with BB versus placebo (n = 347; SMD, −0.54; 95% CI, −0.90 to −0.18; P = 0.003) (Fig. 3).

TABLE 3. Exercise testing methodology and peak cardiorespiratory variables in studies included in the meta-analysis.

				HR_{peak}, bpm[a]		$\dot{V}_{Epeak}$ (L·min^{-1})[a]	
Reference	Ergometer	Position	Increment Rate	BB	PBO	BB	PBO
Conraads et al. (17)	Bicycle	Upright	20 W every 2 min	127 ± 24	132 ± 21	n/a	n/a
Norozi et al. (18)	Bicycle	Upright	0.5 W·kg^{-1} every 2 min	161 ± 21	159 ± 23	n/a	n/a
Terzi et al. (19)	Treadmill	Upright	2 km·h^{-1} every 1 min	143 ± 21	149 ± 26	40 ± 13	37 ± 11
Dubach et al. (20)	Bicycle	Upright	Individualized to elicit $\dot{V}O_{2peak}$ in ~10 min	144 ± 20	146 ± 17	55 ± 13	53 ± 14
Gullestad et al. (22)	Bicycle	Upright	20 W every 2 min	141 ± 26	133 ± 30	49 ± 16	45 ± 11
Hulsmann et al. (21)	Bicycle	Upright	Individualized	n/a	n/a	n/a	n/a
Genth-Zotz et al. (23)	Bicycle	Semi-supine	10 W every 1 min	123 ± 18	121 ± 24	42 ± 12	44 ± 12
Guazzi et al. (24)	Bicycle	Upright	Individualized to elicit $\dot{V}O_{2peak}$ in ~10 min	n/a	n/a	54 ± 6	55 ± 6
Gilbert et al. (25)	Treadmill	Upright	3.5% grade every 2 min	n/a	n/a	n/a	n/a
Krum et al. (27)	Bicycle	Upright	n/a	n/a	n/a	n/a	n/a
Olsen et al. (26)	Bicycle	Upright	5–10 W every 1 min	152 ± 23	158 ± 24	n/a	n/a
Metra et al. (28)	Bicycle	Upright	20 W every 2 min	144 ± 21	155 ± 21	n/a	n/a
Woodley et al. A (29)	Treadmill	Upright	3.5% grade every 2 min	163 ± 22	149 ± 21	n/a	n/a
Woodley et al. B (29)	Treadmill	Upright	3.5% grade every 2 min	145 ± 23[b]	136 ± 28[b]	n/a	n/a

Data are mean ± SD.
[a]Baseline data.
[b]Data from primary sample size.
n/a, data not available; PBO, placebo group; $\dot{V}_{Epeak}$, peak minute ventilation.

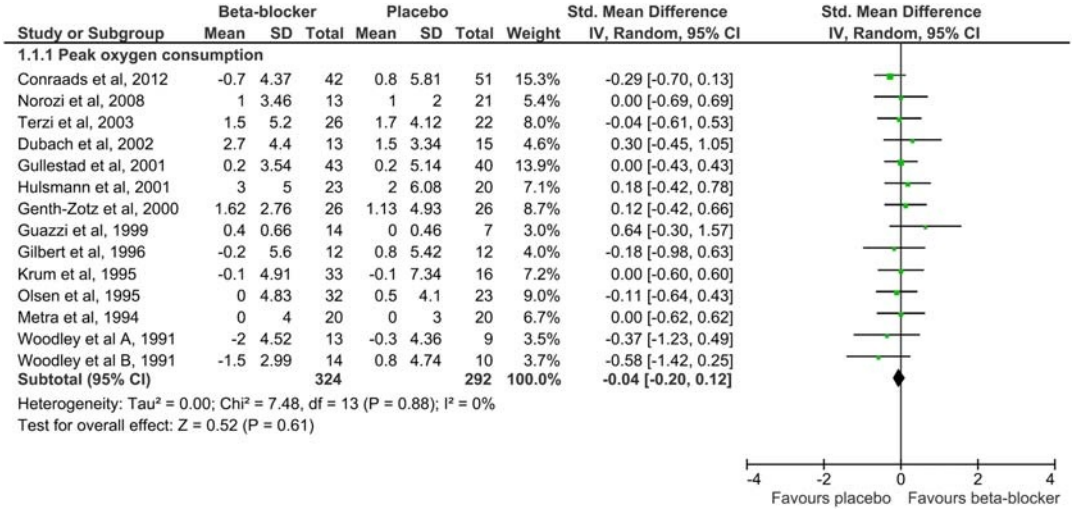

FIGURE 1—Forest plot of the SMD between the effects of BB and placebo treatment on $\dot{V}O_{2peak}$ in HF patients. *Squares* represent the SMD for each study. *Diamonds* represent the pooled SMD across studies. *df*, degrees of freedom; IV, inverse variance; SD, standard deviation.

Methodological quality assessment and potential bias. The methodological quality of the studies was moderate to high (see Table, Supplemental Digital Content 3, Quality assessment of studies included in the meta-analysis, http://links.lww.com/MSS/B131). The average Jadad score (49) was 3.0 ± 0.8 out of a possible 5 points, ranging from 2 to 4 points. All studies were RCT, 13 of them reported as double-blind trials. Nine studies had adequately described dropouts, whereas the rest did not comment on dropouts. With respect to the evaluation of potential biases, the Begg and Mazumdar rank correlation test ($P = 0.91$), Egger regression test ($P = 0.51$), and the funnel plot (see Figure, Supplemental Digital Content 4, Funnel plot of the SMD in $\dot{V}O_{2peak}$, http://links.lww.com/MSS/B132) (52,53) did not suggest the presence of publication bias and/or other biases regarding the SMD in $\dot{V}O_{2peak}$ in the studies included in the meta-analysis.

DISCUSSION

In this systematic review and meta-analysis, we pooled and analyzed data from 14 RCT studies assessing the effect of BB interventions ranging from 3 to 24 months of duration on $\dot{V}O_{2peak}$ in a total of 616 HF patients. The main finding of this meta-analysis is that prolonged BB administration does not affect $\dot{V}O_{2peak}$, an outcome that was remarkably consistent across varied BB intervention characteristics. Likewise, peak exercise performance remained unaltered, albeit NYHA functional class was improved with BB treatment.

A therapy may be judged thoroughly successful if it prolongs and ameliorates the quality of life. Functional gains are particularly relevant in the context of disease such as HF in which treatment-induced increases in longevity are exiguous (15,54). That BB administration attenuates hemodynamic stress and blunts chronotropic responsiveness suggests a limitation of cardiac pumping capacity and thereby $\dot{V}O_{2peak}$. Results from this meta-analysis indicate that $\dot{V}O_{2peak}$ is preserved with prolonged BB treatment, although marked decrements in HR_{peak} were noted in most of the studies (17–20,22–24,26,28,29). Hence, BB may induce compensating adaptations in ventricular function enhancing SV to maintain cardiac output and convective

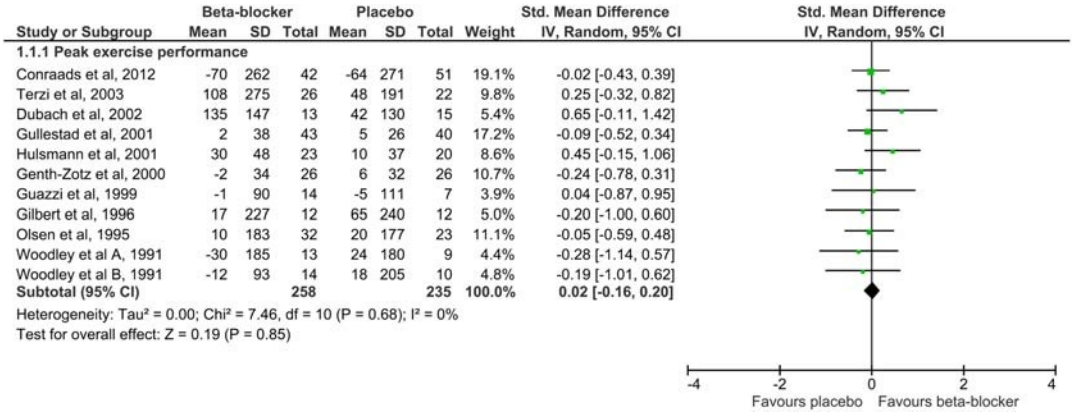

FIGURE 2—Forest plot of the SMD between the effects of BB and placebo treatment on peak exercise performance in HF patients. *Squares* represent the SMD for each study. *Diamonds* represent the pooled SMD across studies. *df*, degrees of freedom; IV, inverse variance; SD, standard deviation.

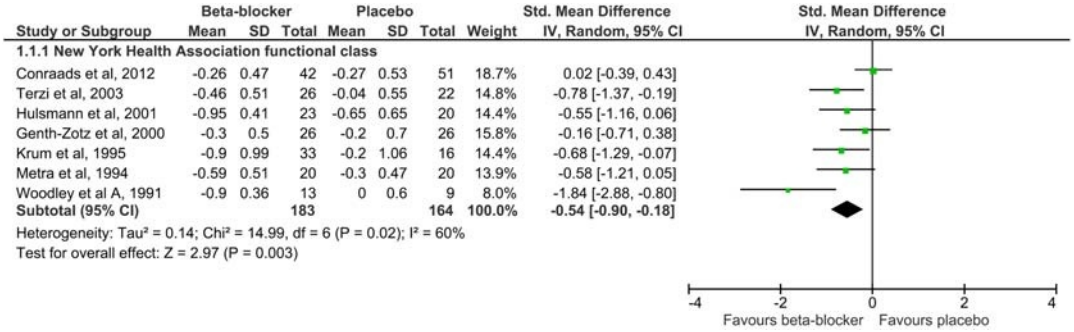

FIGURE 3—Forest plot of the SMD between the effects of BB and placebo treatment on NYHA functional class in HF patients. *Squares* represent the SMD for each study. *Diamonds* represent the pooled SMD across studies. *df*, degrees of freedom; IV, inverse variance; SD, standard deviation.

O_2 delivery (23,24). Indeed, resting LVEF increased by 6%–18% with BB treatment (20,21,23–25,27–29). Limited evidence denotes similar BB-related improvements in LVEF at peak exercise or with atrial pacing (23,55). Underlying mechanisms can include a partial reversal of ventricular remodeling (24,56) and improved myocardial metabolism (57,58) leading to reduced filling pressure/SV ratio implying a shift in the operating point to a steeper portion of the Frank–Starling curve (57). In addition, the robust effect of BB on $\dot{V}O_{2peak}$ should be remarked as demonstrated by the null heterogeneity among studies involving distinct intervention features as regards BB agent, type, target dose, and duration. This suggests the presence of a generalized homeostatic regulation of cardiac output in response to prolonged BB treatment in HF.

Beta-adrenergic blockade may interfere with skeletal muscle metabolism during exercise (59). β_1-Selective BB and nonselective BB inhibit lypolysis (60), whereas nonselective BB specifically decreases energy flux through glycogenolysis, leading to delayed glycolysis (61,62). This implies a limitation of muscle contraction at high exercise intensities, known to primarily depend on glycolysis for energy production (63). The negative influence of acute BB administration on peak exercise performance has been previously described in healthy individuals, being more pronounced with nonselective than with β_1-selective BB (60). In contrast, short-term ($\leq$1 wk) BB administration does to affect incremental exercise time in HF patients, irrespective of type of BB (28,64,65). Similarly, in the present meta-analysis, peak exercise performance remained consistently unaltered after prolonged BB treatment. The divergence between healthy individuals and HF patients could be related to intrinsic abnormalities in skeletal muscle metabolism. Exercising skeletal muscle in HF patients is characterized by the overactivation of glycogenolysis associated with an earlier shift to glycolytic metabolism expediting muscle dysfunction (66). This might be partially corrected by nonselective BB, facilitated by the aforementioned retardation of glucose metabolism (67). Furthermore, nonselective BB and β_1-selective BB prevent muscle atrophy, thus lessening the recession of muscle cross-sectional area and strength in HF patients (68,69).

At variance with measures of exercise capacity, NYHA functional class was improved by BB treatment. In the NYHA scheme, patients are classified into four categories ordered from least to most severe HF according to the extent of symptoms (shortness of breath, angina) at rest and during habitual physical activity (70). Notwithstanding the subjective nature of this assessment, BB-induced reduction of NYHA functional class could be attributed to changes in ventilation, which for a given work rate is inappropriately increased in HF patients because of augmented ergoflex and chemoreflex. Substantial decreases (up to 20% decrements) in ventilation during submaximal exercise have been reported in HF patients after nonselective and β_1-selective BB treatment (71,72). BB may enhance ventilatory efficiency by decreasing the ventilation/carbon dioxide output slope (71), although this is not a universal finding (24,73). Alternatively, stimuli that activate ventilation such as carbon dioxide output and muscle acidosis could be reduced by nonselective BB through the aforementioned limitation of skeletal muscle glycolytic metabolism and lactate production (73,74). Ultimately, the effects of BB on ventilation may translate into improved symptoms derived from the attenuation of breathing discomfort and the early feeling of fatigue, which are partly dissociated from $\dot{V}O_{2peak}$ (75,76).

LIMITATIONS

First, most of the studies included patients with HF and reduced LVEF (<40%), which approximately comprise half of the HF population; thus, our conclusions should be confined accordingly. The exclusion of the two studies including patients with HF and preserved LVEF did not alter the SMD in $\dot{V}O_{2peak}$ (SMD, 0.00; P = 0.99), peak exercise performance (SMD, 0.03; P = 0.79), and NYHA functional class (SMD, −0.65; P < 0.001) (17,18). Second, BB effects could be influenced by concomitant standard HF pharmacotherapy. Nonetheless, heterogeneity statistics did not reveal any moderating effect of reported medications, and the SMD in $\dot{V}O_{2peak}$ was rather uniform among studies. Third, one study did not explicitly report the use of placebo in the control group (19). The exclusion of this study did not alter the results of this meta-analysis. Finally, the mean

methodological quality of the included studies was determined as moderate to high, and no publication bias and/or other biases were detected.

CONCLUSIONS

The current meta-analysis demonstrates that $\dot{V}O_{2peak}$ is preserved with BB treatment in HF patients. Moreover, although $\dot{V}O_{2peak}$ and peak exercise performance remained unaltered, BB treatment elicited positive effects in the functional status determined by the NYHA functional class, possibly attributed to reduced ventilatory overactivation. These findings contribute to clarify the effect of BB administration on exercise capacity and symptom relief in patients with HF.

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